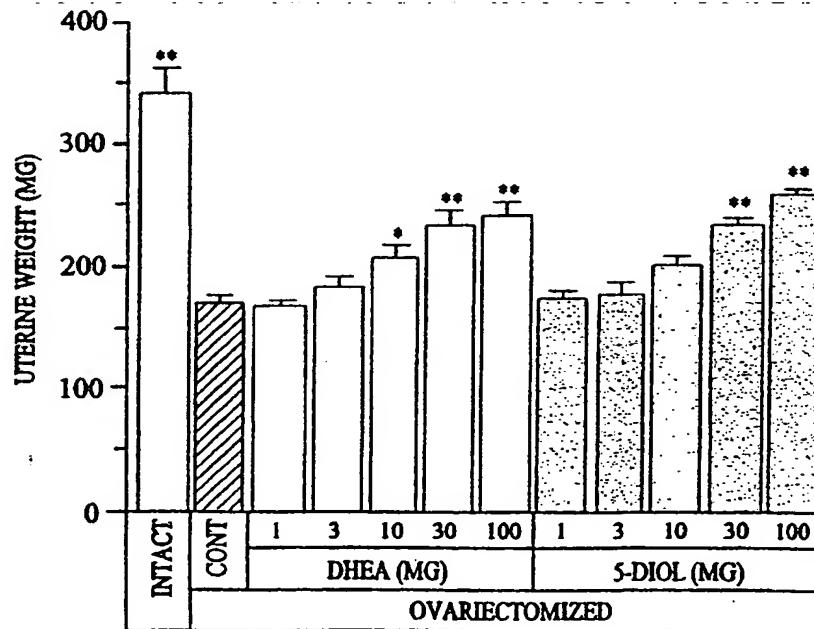




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(30) Priority Data: 09/096,286 11 June 1998 (11.06.98) US			
(71) Applicant: ENDORECHERCHE, INC. [CA/CA]; 2989 de la Promenade, Ste-Foy, Quebec G1W 2J5 (CA). (72) Inventor: LABRIE, Fernand; 2989 de la Promenade, Ste-Foy, Quebec G1W 2J5 (CA).		Published With international search report.	
(74) Agent: MITCHELL, Richard, J.; Marks & Clerk, P.O. Box 957, Station B, Ottawa, Ontario K1P 5S7 (CA).		(88) Date of publication of the international search report: 2 November 2000 (02.11.00)	

(54) Title: PHARMACEUTICAL COMPOSITIONS AND USES FOR ANDROST-5-ENE-3 β ,17 β -DIOL

(57) Abstract

Androst-5-ene-3 β ,17 β diol is used to treat or reduce the likelihood of acquiring osteoporosis or menopausal symptoms, or other diseases affected by estrogen receptor activity, like vaginal atrophy, hypogonadism, diminished libido, skin atrophy, urinary incontinence, ovarian cancer, uterine cancer, endometriosis, obesity, cardiovascular disease, loss of muscle mass, loss of energy or fatigue, Alzheimer's disease and loss of memory and for conditions which respond well to DHEA treatment, but where a higher ratio of estrogenic to androgenic effects is desired. Combination therapies are included, as are kits and pharmaceutical compositions for providing the active ingredients of claimed methods and combinations.

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INTERNATIONAL SEARCH REPORT

Int'l. Appl. No.

PCT/CA 99/00537

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 16709 A (ENDORECHERCHE INC) 4 August 1994 (1994-08-04)	1
A	abstract page 21, line 12 -page 38, line 3; claims 1-28	24
P, X	WO 98 56386 A (CAMPONOVO TIZIANO ;SUNNIMEX LTD (GB)) 17 December 1998 (1998-12-17)	1-4, 6-8, 10, 13-15, 25-27
	abstract page 3, line 3 -page 12, line 4; claims 1-13	
X	US 5 387 583 A (LORIA ROGER M) 7 February 1995 (1995-02-07) abstract; claims 1-7	1-8, 26, 27
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

7 August 2000

Date of mailing of the international search report

16.08.00

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INTERNATIONAL SEARCH REPORT

b. National Application No
PCT/CA 99/00537

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 206 008 A (LORIA ROGER) 27 April 1993 (1993-04-27) abstract column 3, line 62 -column 5, line 68; examples 1-5 column 12, line 48 -column 14, line 40 ---	1-8, 25-27
X	FR 672 M (VISMARA) 17 July 1961 (1961-07-17) page 1, column 1, line 1 -page 2, column 1, line 41 ---	1,6,7, 23,25,27
X	US 5 461 042 A (LORIA ROGER M) 24 October 1995 (1995-10-24) abstract column 2, line 40 -column 4, line 35; claims 1-16; examples 1-12 ---	1-9, 25-27
X	C E BIRD ET AL: "Delta5-androstenediol: kinetics of metabolism and binding to plasma proteins in normal post-menopausal women" ACTA ENDOCRINOLOGICA, NO. SCANDINAVIAN UNIVERSITY PRESS, OSLO, vol. 99, no. 2, page 309-313 XP002082225 ISSN: 0001-5598 page 312, column 1, paragraph 4 -column 2, paragraph 1 ---	17,18,23
X	DAUVOIS S ET AL: "ANDROSTENEDIONE AND ANDROST-5-ENE-3BETA,17BETA-DIOL STIMULATE DMBA-INDUCED RAT MAMMARY TUMORS - ROLE OF AROMATASE" BREAST CANCER RESEARCH AND TREATMENT, US, NIJHOFF, BOSTON, vol. 13, no. 1, page 61-69 XP000863496 ISSN: 0167-6806 abstract ---	23
X	TOURNIAIRE: "les limites de l'androgenotherapie" CAH. MED., vol. 15, no. 9, 1974, pages 583-588, XP002129030 abstract page 584, column 2, paragraphs 1-5 page 587, column 1, paragraph 1 ---	1,12
A	ARANEO ET A.: "Dehydroepiandrosterone reduces progressive dermal ischemia caused by thermal injury" J. SURG. RES., vol. 59, no. 2, 1995, pages 250-262, XP002129031 table 1 ---	1,15

-/-

INTERNATIONAL SEARCH REPORT

In ..ational Application No
PCT/CA 99/00537

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUIPER ET AL.: "The Estrogen Receptor beta Subtype: A Novel Mediator of Estrogen Action in Neuroendocrine Systems" FRONTIERS IN NEUROENDOCRINOLOGY, vol. 19, no. 4, 1998, pages 253-286, XP002129032 abstract; figure 4; table 1 page 276, paragraph 5 -page 277, paragraph 1 ---	1-8,25
X	EP 0 424 954 A (NIPPON ZOKI PHARMACEUTICAL CO) 2 May 1991 (1991-05-02) abstract page 1, line 37-47 ---	1-8,13
X	DORGAN J F ET AL: "Relationship of serum dehydroepiandrosterone (DHEA), DHEA sulfate, and 5-androstene-3 beta, 17 beta-diol to risk of breast cancer in postmenopausal women." CANCER EPIDEMIOLOGY, BIOMARKERS AND PREVENTION, (1997 MAR) 6 (3) 177-81., XP002129033 abstract ---	1,23
X	YOSHIMOTO S ET AL: "Clinical effects of metharmon F for postmenopausal women with climacteric symptoms: its relationship with serum level of hormones." HORUMON TO RINSHO. CLINICAL ENDOCRINOLOGY, (1983 AUG) 31 (8) 815-22., XP002129034 the whole document ---	1-10,14
X	LUO, S.; SOURLA, A.; LABRIE, C.; BELANGER, A.; LABRIE, F.: "Effects of combination of dehydroepiandrosterone and EM-800 on bone mass, serum lipids, and the development of dimethylbenz(A)anthracene (DMBA)-induced mammary carcinoma in the rat." BREAST CANCER RESEARCH AND TREATMENT, vol. 46, no. 1, 1997, page 55 XP000921456 abstract ---	24
X	COUILLARD, S.; LABRIE, C.; GAUTHIER, S.; LABRIE, F.: "Inhibitory effect of a new non-steroidal pure antiestrogen (EM-800) in combination with DHEA on human ZR-75-1 breast tumors in nude mice." MATURITAS, vol. 27, no. suppl., 1997, page 80 XP000922606 abstract ---	24

INTERNATIONAL SEARCH REPORT

In. ..ational Application No
PCT/CA 99/00537

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LUO, SHOUQI; SOURLA, ANTIGONE; LABRIE, CLAUDE; BELANGER, ALAIN; LABRIE, FERNAND: "Combined effects of dehydroepiandrosterone and EM-800 on bone mass, serum lipids, and the development of dimethylbenz(A)anthracene-induced mammary carcinoma in the rat." ENDOCRINOLOGY, vol. 138, no. 10, 1997, pages 4435-4444, XP000921482 abstract	24
X	PASQUALINI J.R.: "Role of androgens in breast cancer." JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, vol. 45, no. 1-3, - 1993 pages 167-172, XP000921485 abstract page 170, column 2	24
X	WO 97 03676 A (CABO SOLER JOSE ;CALDERON GOMEZ JESUS (ES); PALACIOS GIL ANTUNANO) 6 February 1997 (1997-02-06) abstract page 3, line 24-31	24
X	BOCCUZZI G; DI MONACO M; BRIGNARDELLO E; LEONARDI L; GATTO V; PIZZINI A; GALLO M: "Dehydroepiandrosterone antiestrogenic action through androgen receptor in MCF-7 human breast-cancer cell line." ANTICANCER RESEARCH, vol. 13, no. 6a, 1993, pages 2267-2272, XP000921483 abstract	24
X	DOWSETT M.; CANTWELL B.; LAL A.; JEFFCOATE S.L.; HARRIS A.L.: "Suppression of postmenopausal ovarian steroidogenesis with the luteinizing hormone - releasing hormone agonist goserelin." JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 66, no. 4, 1988, pages 672-677, XP000923071 abstract page 672, column 1 -column 2, paragraph 1 page 676, column 1, paragraph 4 -column 2, paragraph 2	24

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00537

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MEYSKENS F L: "STRATEGY FOR CHEMOPREVENTION OF HUMAN BREAST CANCER." CANCER INVEST., vol. 6, no. 5, 1988, pages 609-614, XP000923070 table 1 ---	24
A	WO 93 16704 A (UNIV EAST CAROLINA) 2 September 1993 (1993-09-02) abstract ---	24

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International application No.
PCT/CA 99/00537

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.: _____
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: _____

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-23,25-27

Pharmaceutical compositions and their use (i) in the treatment of symptoms of menopause, vaginal atrophy, hypogonadism, osteoporosis, diminished libido, skin atrophy, urinary incontinence, ovarian cancer, uterine cancer, skin dryness, endometriosis, obesity, cardiovascular disease, atherosclerosis, insulin resistance, loss of muscle mass, loss of energy or fatigue, Alzheimer disease, (ii) in a method of contraception.

2. Claim : 24

Use of dehydroepiandrosterone in association with other compounds as defined in claim 24 in the treatment of breast cancer, uterine cancer, ovarian cancer or endometriosis.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 24 relates to a product/compound/method defined by reference to a desirable characteristic or property, namely antiestrogen, androgenm inhibitor of aromatase, inhibitor of 17beta hydroxsteroid dehydrogenase, LHRH agonist or antagonist.

The claims cover all products/compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds/methods as disclosed on page 22, paragraph 2 of the description.

The term "pro-drug" is not clear in the present context since it is not clear which compounds are metabolised by or in the human body into the mentioned compound.

The term "treating or reducing the likelihood of acquiring reduced or imbalanced concentrations of sex steroids" is not clear in relation to a therapeutic use because it is not exhaustively known which diseases are associated with reduced or imbalanced concentrations of sex steroids.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte lational Application No

PCT/CA 99/00537

Patent document cited in search report	Publication date		Patent family member(s)	Publication date	
WO 9416709 A	04-08-1994		US 5776923 A AU 686120 B AU 5388494 A AU 5855794 A CA 2154161 A CN 1116823 A CZ 9501565 A EP 0680327 A FI 953017 A HU 73241 A JP 8505629 T NO 952417 A NZ 250712 A SK 77995 A US 5843932 A US 5798347 A US 5854229 A US 5728688 A US 5824671 A US 5872114 A US 5837700 A US 5948434 A US 5922700 A US 5780460 A US 5807849 A US 5955455 A ZA 9400372 A		07-07-1998 05-02-1998 28-07-1994 15-08-1994 04-08-1994 14-02-1996 13-12-1995 08-11-1995 19-06-1995 29-07-1996 18-06-1996 16-06-1995 26-11-1996 09-04-1997 01-12-1998 25-08-1998 29-12-1998 17-03-1998 20-10-1998 16-02-1999 17-11-1998 07-09-1999 13-07-1999 14-07-1998 15-09-1998 21-09-1999 19-07-1995
WO 9856386 A	17-12-1998		IT MI971372 A AU 7918798 A	11-12-1998 30-12-1998	
US 5387583 A	07-02-1995		WO 9423722 A	27-10-1994	
US 5206008 A	27-04-1993		AU 2265092 A EP 0637203 A WO 9320696 A US 5277907 A US 5461042 A US 5641768 A	18-11-1993 08-02-1995 28-10-1993 11-01-1994 24-10-1995 24-06-1997	
FR 672 M			NONE		
US 5461042 A	24-10-1995		US 5277907 A US 5077284 A US 5641768 A AU 2265092 A EP 0637203 A WO 9320696 A US 5206008 A US 5407684 A	11-01-1994 31-12-1991 24-06-1997 18-11-1993 08-02-1995 28-10-1993 27-04-1993 18-04-1995	
EP 0424954 A	02-05-1991		AT 104854 T DE 69008476 D DE 69008476 T ES 2055845 T JP 3209328 A US 5116828 A	15-05-1994 01-06-1994 01-09-1994 01-09-1994 12-09-1991 26-05-1992	

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No

PCT/CA 99/00537

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9703676	A	06-02-1997	ES	2098193 A	16-04-1997
			AU	6419696 A	18-02-1997

WO 9316704	A	02-09-1993	AT	193447 T	15-06-2000
			AU	676470 B	13-03-1997
			AU	3731793 A	13-09-1993
			CA	2117532 A	02-09-1993
			DE	69328771 D	06-07-2000
			EP	0627921 A	14-12-1994
			JP	7504198 T	11-05-1995
			US	5527789 A	18-06-1996